UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P O Box 1450
Alexandria, Virginia 22313-1450
www uspto gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,495	01/13/2005	Gerard O'Beirne	PA0248	2631

22840 7590 08/26/2010
GE HEALTHCARE BIO-SCIENCES CORP.
PATENT DEPARTMENT
101 CARNEGIE CENTER
PRINCETON, NJ 08540

EXAMINER	
BOESEN, CHRISTIAN C	

ART UNIT	PAPER NUMBER
1639	

NOTIFICATION DATE	DELIVERY MODE
08/26/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

LSUSPatents@ge.com

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/521,495
Filing Date: January 13, 2005
Appellant(s): O'BEIRNE ET AL.

Yonggang Ji (Registration number 53,073)
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 07/16/2010 appealing from the Office action mailed 11/17/2009.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

The following is a listing of the evidence (e.g., patents, publications, Official Notice, and admitted prior art) relied upon in the rejection of claims under appeal.

Thastrup (10/15/1998) PCT International Patent Application Publication WO 98/45704 A2

Bastiaens (02/17/2000) PCT International Patent Application Publication WO 00/08054 A1

Gonye (10/25/2001) PCT International Patent Application Publication WO 01/79419 A2

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Appellant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Thastrup

4. Claims 1, 3, 4, 6, 7, 9-11 and 16-19 are rejected under 35 U.S.C. **102(b)** as anticipated by or, in the alternative, under 35 U.S.C. **103(a)** as obvious over **Thastrup** et al (WO 98/45704; 1998; cited in IDS). This rejection is necessitated by Appellant's amendments to the claims.

The instant claims recite "A method for determining the function of one or more effector nucleic acid sequences from a library of effector nucleic acid sequences comprising:

i) determining the distribution of a detectable label expressed from one of a group of indicator nucleic acid sequences expressed in cells in both the presence and the absence of a group of chemical modulators, which affect said distribution of said detectable label, wherein the cells express one of said effector nucleic acid sequences;

ii) repeat step i) with a different effector nucleic acid sequence from said library of effector nucleic acid sequences;

iii) analyzing the distribution data of said detectable label from all combinations of said effectors, modulator and indicator to derive functional linkages among said effecotrs, modulator and indicator; and

iv) repeating steps i) to iii) with different combinations of effector nucleic acid sequences, chemical modulators and indicator nucleic acid sequences until a function is assigned successfully to said one or more effector nucleic acid sequences."

Thastrup et al, throughout the publication, teach methods of using various genetic materials, compounds and cells to assay for molecular functions inside cells. (e.g. Abstract).

For claim 1: The preamble of the instant claim only recites intended use of the claimed method and does not provide additional structural limitations. See MPEP 2111.02.

Step i): The reference teaches inserting a DNA molecule encoding for a fusion protein comprising "GFP" and another protein (such as a protein kinase) into cells (e.g. Examples; pp.34+), which the GFP encoding DNA reads on the "<u>indicator</u> nucleic acid" as the term is broadly defined in the instant specification (p.7). The portion of the DNA that encodes for other protein (such as the protein kinase) of the fusion protein read on the "<u>effector</u> nucleic acid sequence" as the term is broadly defined in the instant specification (p.7). The reference also teaches testing the cells in the presence and absence of at least two other molecules including "forskolin" and "norepinephrine" (e.g. p.35, lines 4+), which the "forskolin" or "norepinephrine" reads on "chemical <u>modulator</u>" and as the term "modulator" is broadly defined in the instant specification (p.7).

Step ii): The reference teaches "repeating" the same assay using different effector/indicator constructs having different "effector" such as various kinases PKA, PKC, Erk1, or phosphatases, etc. (e.g. pp.35+; Examples; pp.10+).

Step iii): The reference also teaches detecting the cellular localization of the GFP signals (e.g. p.35, lines 6+), which reads on the "analyzing the distribution of said detectable label" as recited in step iii).

The reference also teaches measuring the "distribution" or localization of the GFP signal in cells before and after addition (or stimulation) of compounds (such as forskolin, norepinephrine, and carbachol) using digital imaging system (e.g. pp.35-36; Figures 3, 7 and 8). The reference teaches comparing the distribution data with stimulation to without stimulation using graphic representations, and digital imaging (e.g. pp.35+).

The reference also teaches analyzing the distribution data and assessing the "stimulatory" effects of either forskolin or norepinephrine (e.g. p.35; Figure 3H). The reference also teaches the function of the protein kinase (i.e. the "effector") by measuring the amount cAMP (e.g. p.35, lines 10+), and thus assigning kinase function of the protein kinase (i.e. detecting "functional linkage" or assigning function). Therefore, the "functional linkage" among the effector (such as the kinase), modulator (such as forskolin) and the indicator (GFP) can be derived.

Step iv): The reference teaches "repeating" the same assay using different effector/indicator constructs having different "effector" such as various kinases PKA, PKC, Erk1, or phosphatases, etc. (e.g. pp.35+; Examples; pp.10+). The reference also teaches measuring/detecting/analyzing for each of the combinations of components (e.g. pp.35-36; Figures 3, 7 and 8; Examples).

For claim 3: The DNA that encodes for other protein (such as the protein kinase) of the fusion protein read on the "<u>effector</u> nucleic acid sequence" as the term is broadly defined in the instant specification (p.7).

For claim 4: The reference teaches transfecting plasmid containing nucleic acids encoding for a fusion protein (e.g. p.31, lines 1+), which the transfected plasmid (containing double stranded DNA) inherently comprises "an antisense oligonucleotide". An antisense oligonucleotide is the complementary strand of the sense stand (see attached Definition for Antisense downloaded from Merriam-Webster Online Dictionary on 5/8/08). That is any portion (such as a 20 nucleotide portion) of the complementary strand in the plasmid encoding for a protein (such as the protein kinase) read on "an antisense oligonucleotide", because the complementary strand would be "complementary to a segment of genetic material" (i.e. complementary to the sense strand, for example).

For claim 6: The reference teaches expression vectors comprising DNA encoding for the fusion proteins (e.g. pp.30-31).

For claim 7: The reference teaches plasmid expression vectors containing the fusion protein (e.g. pp.30-31).

For claim 8: The reference teaches using GFP (green fluorescent protein) and detecting the fluorescent signals (e.g. pp.36-37), which the GFP reads on a detectable label.

For claim 9: The reference teaches inserting a DNA molecule encoding for a fusion protein comprising "GFP" (reads on the "indicator") and another protein (such as a protein kinase) (reads on the "effector") into cells (e.g. Examples; pp.34+).

For claim 10: The reference teaches using GFP (green fluorescent protein) and detecting the fluorescent signals (e.g. pp.36-37).

For claim 11: The reference teaches using mutant GFP with at least a S65T mutation (e.g. p.30, lines 11+; p.7).

For claim 16: The reference teaches using various cells such as Chinese hamster ovary cells (e.g. p.31, lines 7+), which reads on the eukaryotic cells.

For claim 17: The reference teaches using various cells such as Chinese hamster ovary cells (e.g. p.31, lines 7+) as well as mammalian cells (e.g. pp.5+).

For claim 18: The reference also teaches using cells such as "HUVEC" (human umbilical vein endothelial cells) (e.g. p.22, lines 24+), which reads on the human cells.

For claim 19: The reference teaches using digital imaging system (e.g. pp.35-36; Figures 3, 7 and 8).

Alternatively, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to repeat the same cell based assay with fusion proteins comprising different proteins (effectors) and modulators. Thastrup et al, teach using commercially available cDNA libraries to generate genes of interest (such as "effector nucleic acid sequences") (e.g. p.14, lines 15+). The reference also teaches generating fusion proteins based on GFP and any gene of interest (e.g. pp.13-14). The Thastrup reference also teaches screening library of compounds (such as a library of "chemical modulators") in cell based assays with GFP fusion proteins (e.g. p.7, lines 15+; p.20, lines 11+). The Thastrup reference explicitly states "contacting or incubating the cell or cells with substances… to exert and influence on the cellular response involving a re-distribution contribution", and the "influence could be substances from a compound drug library". (e.g. p.20, lines 15+).

In addition, it would have been obvious to one skilled in the art to substitute one protein of interest in the fusion protein for the other, or substitute one modulator for the other to achieve

the predictable result of "repeating" the same cell based assay with different combination(s) of components (effectors, indicators, etc) as the Thastrup reference teaches the advantages of such screening system. It would have been obvious to one of ordinary skill in the art to apply the standard technique of repeatedly using a reporter based cell system to analyze protein-protein, and protein-chemical interactions in cells as taught by Thastrup, to improve cell based assay and analysis for the predicable result of enabling standard analysis of the functional relationships among proteins and their modulators.

Thastrup and Bastiaens

5. Claims 1, 3, 4, 6, 7, 9-12 and 16-19 are rejected under 35 U.S.C. **103(a)** as being unpatentable over **Thastrup** et al (WO 98/45704; 1998; cited in IDS), in view of **Bastiaens** et al. (WO 00/08054; 2/17/2000; cited previously).

Thastrup et al, throughout the publication, teach methods of using various genetic materials, compounds and cells to assay for molecular functions inside cells, as discussed supra. The above rejection over Thastrup is hereby incorporated by reference in its entirety.

Thastrup et al do not explicitly teach the modified GFP has three mutations as recited in **clm 12**.

However, **Bastiaens** et al, throughout the publication, teach various GFP mutants (e.g. Abstract). The reference teaches a GFP mutant (e.g. "YFP5" or "MmGFP5") with mutations including F64L, S65T and S175G (e.g. p.20, Table 1), which read on the GFP mutant as recited in **clm 12**. The reference also teaches the advantages of such GFP mutants including providing a mutant with fluorescent at a unique wavelength (i.e. a red-shifted mutant) (e.g. p.17, lines 1+),

longer lifetime, and provides a fluorescent label for multi-labelling experiments (e.g. p.19, lines 5+).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to use a GFP mutant with the F64L, S65T and S175G mutations for signaling indicator.

A person of ordinary skill in the art would have been motivated at the time of the invention to use a mutant GFP with F64L, S65T and S175G mutations in a screening assay in cells, because Bastiaens et al teaches the advantages of such GFP mutants including providing a mutant with fluorescent at a unique wavelength (i.e. a red-shifted mutant) (e.g. p.17, lines 1+), longer lifetime, and provides a fluorescent label for multi-labelling experiments. Because both of the Thastrup and the Bastiaens references teach methods of expressing GFP mutant proteins, it would have been obvious to one skilled in the art to substitute one GFP mutant for the other to achieve the predictable result of expressing GFP mutants for detecting fluorescent signals.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since both Thastrup and Bastiaens references have demonstrated the success of using various GFP mutants for cellular screening assays.

Thastrup and Others

6. Claims 1, 3, 4, 6, 7, 9-12 and 16-19 are rejected under 35 U.S.C. **103(a)** as being unpatentable over **Thastrup** et al (WO 98/45704; 1998; cited in IDS), in view of **Bastiaens** et al. (WO 00/08054; 2/17/2000; cited previously), and if necessary, in view of **Gonye** et al. (WO 01/79419; 10/25/01; cited in IDS).

Thastrup et al, throughout the publication, teach methods of using various genetic materials, compounds and cells to assay for molecular functions inside cells, as discussed supra.

Bastiaens et al, throughout the publication, teach various GFP mutants, as discussed supra.

The combination of the Thastrup and Bastiaens teachings as discussed supra is hereby incorporated by reference in its entirety.

Gonye et al, throughout the publication, teach using various reporter fusion protein to provide genomic wide analysis (e.g. Abstract). The reference teaches analyzing genes of the whole genome and comparing data between genomic analysis (e.g. claims). The reference also teaches identifying and determining functions of the genes (e.g. Abstract; claims)

Therefore, it would have been obvious to one of ordinary skill in the art to apply the standard technique of repeatedly using a reporter based cell system to analyze protein-protein, and protein-chemical interactions in cells for genomic wide analysis, to improve cell based assay and analysis for the predicable result of enabling standard analysis of the functional relationships among proteins and their modulators.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since both Thastrup, Bastiaens and Gonye references have demonstrated the success of using various GFP mutants for cellular screening assays.

(10) Response to Argument

Appellant's arguments have been fully considered but fail to persuade.

The Appellant argues that claim 1 requires three components: 1) an indicator, 2) a modulator, and 3) an effector (appeal brief page 5 bottom). The Appellant argues that Thastrup only teaches two of the three required elements, specifically, that Thastrup only teaches an indicator and a modulator. Appellant argues that Thastrup does not teach the third element, the effector, and alleges that the PKA-GFP of Thastrup is taken together to be the indicator. The Appellant states

> "Thastrup teaches the use of only two components;
> (i) a GFP fusion protein (e.g. PKA-GFP), which is the equivalent of the indicator in the present invention; and
> (ii) a test substance (e.g. forskolin), which is the equivalent of the modulator in the present invention."

Appeal Brief, page 6, center.

While the Examiner agrees that Appellant's claimed "modulator" reads on the test substances taught in Thastrup (e.g. forskolin), the Examiner disagrees with Appellant's assertion that Thastrup's fusion protein only meets the limitation of the indicator. Instead, the fusion protein of Thastrup, which is made up of a lumiphore ***and*** an intracellular signaling protein, together meet the limitations of the indicator (e.g. GFP) ***and*** effector (e.g. PKA):

> "Cells are genetically modified to expresss **a luminophore**, e.g., a modified (F64L, S65T, Y66H) Green Fluorescent Protein (**GFP**, EGFP) coupled to **a component of an intracellular signalling pathway** such as a transcription factor, a cGMP- or cAMP-dependent protein kinase, a cyclin-, calmodulin- or phospholipid-dependent or mitogen-activated serine/threonin protein kinase, a tyrosine protein kinase, or a protein phosphatase (e.g. **PKA**, PKC, Erk, Smad, VASP, actin, p38, Jnkl, PKG, IkappaB, CDK2, GrkS, Zap70, p85, protein-tyrosine phosphatase lC, Stat5, NFAT, NFkappaB, RhoA, PKB)."

Thastrup abstract.

Thastrup teaches a specific example of two elements that are combined in a fusion protein e.g.,

> "The catalytic subunit of the murine cAMP dependent protein kinase (**PKAc**) was fused C-terminally to a F64L-S65T derivative of **GFP**. The resulting fusion (PKAc-F64L-S65T-GFP) was used for monitoring in vivo the translocation and thereby the activation of PKA."

Thastrup page 30 top.

The Appellant's own specification teaches examples of the claimed indicator-effector as a fusion protein which is made up of a lumiphore ***and*** an intracellular signaling protein. In the Appellant's Example 4 GFP is a lumiphore (*e.g.*, the indicator) and NFκB p65 is an intracellular signaling protein (*e.g.*, the effector).

> "A range of cDNA modulators were transiently transfected into CHO cells expressing a **NFκB p65-GFP fusion protein**."

instant specification Example 4 page 23 lines 30 to 31.

Thastrup teaches expressing the fusion protein inside cells and identifying the location of the fusion protein through the luminophore using a microscope *e.g.*, the unactivated PKAc portion of the fusion protein is located in the cytoplasm by observing the GFP florescence (Thastrup Examples 1 and 2 page 30 line 4 to page 38 line 4). When the fusion protein expressing cells are exposed to a modulator redistribution of the fusion protein can be observed e.g., adding the modulator forskolin to media containing cells expressing the PKAc-GFP fusion protein causes activation of the enzyme adenylyl cyclase and increases the intracellular levels of cAMP; the cAMP activates the PKAc and causes the PKAc to move into the nucleus and interact with CREB; the redistribution of the PKAc-GFP fusion protein is observed by the movement in the GFP florescence signal inside the cell.

For the above reasons, it is believed that the rejections should be sustained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

Respectfully submitted,

/Christian Boesen/
Examiner, Art Unit 1639

Conferees:

/Jeffrey S. Lundgren/
Primary Examiner, Art Unit 1639

/GARY BENZION/
Supervisory Patent Examiner, Art Unit 1637

/ Christopher S. F. Low /
Supervisory Patent Examiner, Art Unit 1636